Combined Use of Bivalirudin and Radial Access in Acute Coronary Syndromes Is Not Superior to the Use of Either One Separately

Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

OBJECTIVES The aim of this meta-analysis was to study the relation between access site and bivalirudin use on outcomes in patients with acute coronary syndrome (ACS).

BACKGROUND Bivalirudin and radial access use are 2 strategies that are increasingly used to lower major bleeding in patients with ACS undergoing invasive approaches. The interaction between these 2 strategies and the benefit of using them in combination are unclear.

METHODS This analysis included randomized controlled trials that compared bivalirudin to heparin with or without glycoprotein IIb/IIIa inhibitors in patients with ACS and reported outcomes stratified by arterial access site. Meta-analyses of outcome data were performed on the basis of access site and anticoagulation regimen. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from event rates using random-effects models.

RESULTS Eight trials with a total of 27,491 patients were included. Bivalirudin reduced major bleeding risk in patients with femoral access (OR: 0.51; 95% CI: 0.46 to 0.6; p < 0.001) but not in patients with radial access (OR: 0.75; 95% CI: 0.45 to 1.26; p = 0.28). Moreover, radial access reduced major bleeding risk in patients treated with heparin (OR: 0.57; 95% CI: 0.43 to 0.77; p < 0.001) but not in patients treated with bivalirudin (OR: 0.96; 95% CI: 0.65 to 1.41; p = 0.83). There were no differences in major adverse cardiovascular events or all-cause mortality between bivalirudin and heparin, regardless of access site.

CONCLUSIONS Bivalirudin reduces bleeding risk only with femoral access, and radial access reduces bleeding risk only with heparin anticoagulation. Therefore, there is no additional benefit to the combined use of bivalirudin and radial access strategies in patients with ACS. (J Am Coll Cardiol Intv 2016;9:1523–31) © 2016 by the American College of Cardiology Foundation.
Inhibitor syndrome(s) cardiovascular event(s) RCT = randomized controlled study evidence interval CI = confidence interval GPI = glycoprotein IIb/IIIa inhibitor MACE = major adverse cardiovascular event(s) OR = odds ratio

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CI = confidence interval
GPI = glycoprotein IIb/IIIa inhibitor
MACE = major adverse cardiovascular event(s)
OR = odds ratio
RCT = randomized controlled trial

The endpoints studied in this meta-analysis were the incidence of major bleeding, major adverse cardiovascular events (MACE), and all-cause mortality at 30 days. Definitions of major bleeding and MACE varied among studies and are shown in Online Table 1. The BRIGHT (Bivalirudin in Acute Myocardial Infarction vs. Heparin and GPI Plus Heparin Trial) study (16) reported bleeding outcomes in patients with radial and femoral access as a combination of major and minor bleeding and therefore was excluded from major bleeding analyses.

Trials were included if: 1) they were RCTs comparing bivalirudin with heparin plus either routine or provisional or bail-out GPIs; 2) they included patients with ACS; 3) 1-month follow-up outcome data were reported; and 4) at least 1 of the studied outcomes was stratified by access site (whether in the original trial publication or in a sub-group analysis published at a later date). Both the ISAR-REACT 4 (Intracoronary Stenting and Antithrombotic Regimen–Rapid Early Action for Coronary Treatment 4) (17) and BRAVE-4 (Bavarian Reperfusion Alternatives Evaluation) (18) trials included <1% patients with radial access and therefore were counted as femoral access-only trials in this meta-analysis.

Trials were excluded if: 1) there was no control group; 2) GPIs were mandated in the bivalirudin arm; 3) anticoagulant agents other than heparin or bivalirudin were used; 4) thrombolytic agents were used; or 5) only balloon angioplasty was done.

DATA EXTRACTION AND QUALITY ASSESSMENT. Data were independently extracted from the included trials by the first and second authors (G.S.M. and G.F.G.) on a pre-specified data sheet. Any discrepancy was discussed until there was complete agreement on all the results in the final data sheet. The potential risk for bias of the RCTs was assessed according to the Cochrane Collaboration guidelines (Online Table 2) (19).

STATISTICAL ANALYSIS. Access-based analysis was performed by comparing outcomes of bivalirudin with those of heparin in femoral and radial access patients. Anticoagulation-based analysis was then performed by comparing outcomes of radial access with those of femoral access in bivalirudin- and heparin-treated patients. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were calculated from rates or percentages using the more conservative DerSimonian and Laird random-effects model (20). All tests were 2 sided, and p values <0.05 were considered to indicate statistical significance. Heterogeneity was assessed using the Cochran Q test and the I² statistic, which describes the percentage of total variation across studies that is due to

Another bleeding-reducing strategy that has been proposed is the use of bivalirudin instead of heparin for anticoagulation (12). Randomized controlled trials (RCTs) have shown that bivalirudin reduces major bleeding compared with heparin plus glycoprotein IIb/IIIa inhibitors (GPIs). However, this bleeding-reducing effect was not evident when GPIs were used selectively in the heparin arm (13,14).

Even though outcomes of bivalirudin and radial access were evaluated separately in many RCTs, it is unclear if there is any additional benefit for using both strategies simultaneously. Therefore, we sought to evaluate, by meta-analysis, the relation between anticoagulation-based analysis and the choice of anticoagulation regimen on outcomes in patients with ACS.

METHODS

The present meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (15).

DATA SOURCE AND SEARCH METHOD. We searched PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for all studies comparing bivalirudin with heparin through December 2015. The following keywords were used: “bivalirudin,” “Angiomax,” “Hirulog,” “heparin,” “acute coronary syndromes,” “ST-elevation myocardial infarction,” “non ST-elevation myocardial infarction,” “unstable angina,” and “percutaneous coronary interventions.” Only studies in English and studies with English translations were included. No other search restrictions were applied. Citations were screened at the title and abstract level, and relevant citations were retrieved as full reports. References of the included trials were also manually searched for relevant studies that might have been missed during the initial search. In addition, the “similar articles” search feature on PubMed was used.

STUDY ENDPOINTS AND SELECTION PROCESS. The endpoints studied in this meta-analysis were the avoidance strategies is essential to improve outcomes in patients with ACS (7).

Given that a substantial portion of bleeding in patients with ACS is related to access site (8), an effective strategy to avoid bleeding is the use of radial access, which is associated with lower major bleeding rates because of the smaller caliber and easier hemostasis of the radial artery compared with the femoral artery (9–11).

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heterogeneity rather than chance (21,22). Potential publication bias was assessed by visual inspection of funnel plots, in which standard errors were plotted against log ORs, as well as Egger’s regression intercept. All statistical analyses were performed using Comprehensive Meta-Analysis version 3 (Biostat, Englewood, New Jersey).

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RESULTS

The present meta-analysis included 8 trials with a total of 27,491 patients. Radial access was used in 8,545 patients and femoral access in 18,946 patients. Bivalirudin was given to 13,364 patients and heparin in 8,545 patients and femoral access in 18,946 patients.

Table 1 lists the detailed characteristics of individual trials included in this meta-analysis. Five trials predominantly included patients with ST-segment elevation myocardial infarction (16,18,23,28,29), 2 trials predominantly included patients with non-ST-segment elevation ACS (17,27), and 1 trial included both groups of patients (11). GPl use was predominantly in the heparin arms in 4 trials (17,27-29), provisional in both arms in 3 trials (11,18,23), and mandated in one heparin arm and not permitted in another heparin arm in one trial (16). The bivalirudin dose was a 0.75-mg/kg bolus followed by 1.75-mg/kg/h infusion in all trials except ACUITY, in which bivalirudin was given as a 0.1-mg/kg bolus and then 0.25-mg/kg/h before angiography, followed by a 0.5-mg/kg bolus before percutaneous coronary intervention and...
continued as a 1.75-mg/kg/h infusion. Heparin was predominantly unfractionated heparin, and the dose varied among trials. The ACUITY trial included patients who received low-molecular weight heparin at a dose of 1 mg/kg twice daily. Details of anticoagulation dosing for all trials are shown in Online Table 3.

ACCESS-BASED ANALYSIS: BIVALIRUDIN VERSUS HEPARIN IN PATIENTS WITH FEMORAL OR RADIAL ACCESS. Major bleeding at 30 days. In patients with femoral access, there was a significant reduction of major bleeding with bivalirudin; 278 of 9,056 patients (3.1%) had major bleeding with bivalirudin compared with 527 of 9,087 patients (5.8%) with heparin with or without GPIs (OR: 0.51; 95% CI: 0.44 to 0.6; p < 0.001; I² = 0%) (Figure 1). In contrast, there was no significant difference in major bleeding between bivalirudin and heparin with or without GPIs in patients with radial access; 49 of 2,675 patients (1.8%) had major bleeding with bivalirudin compared with 68 of 2,676 patients (2.5%) with heparin with or without GPIs (OR: 0.75; 95% CI: 0.45 to 1.26; p = 0.28; I² = 9.5%).

MACE at 30 days. There was no significant difference in incidence of MACE between bivalirudin and heparin with or without GPIs in patients with femoral access and those with radial access (Figure 2). MACE occurred in 790 of 9,386 patients (8.4%) with bivalirudin versus 777 of 9,560 patients (8.1%) with heparin with or without GPIs in the femoral access group (OR: 1.03; 95% CI: 0.93 to 1.14; p = 0.56; I² = 0%) and in 302 of 3,978 patients (7.6%) with bivalirudin versus 318 of 4,567 (7%) with heparin with or without GPIs in the radial access group (OR: 1.07; 95% CI: 0.89 to 1.3; p = 0.47; I² = 9.5%).

All-cause mortality at 30 days. There was no significant difference in mortality between bivalirudin and heparin with or without GPIs in patients with femoral access and those with radial access (Figure 3). In the femoral access group, 131 of 7,501 patients (1.7%) with bivalirudin died versus 137 of 7,519 patients (1.8%) with heparin with or without GPIs (OR: 0.96; 95% CI: 0.75 to 1.24; p = 0.78; I² = 3.07%), and in the radial access group, 42 of
2,675 patients (1.6%) with bivalirudin died versus 48 of 2,678 (1%) with heparin with or without GPIs (OR: 0.95; 95% CI: 0.46 to 1.95; p = 0.89; I² = 37.82%).

**ANTICOAGULATION-BASED ANALYSIS: RADIAL VERSUS FEMORAL ACCESS IN BIVALIRUDIN- AND HEPARIN-TREATED PATIENTS.**

**Major bleeding at 30 days.** In bivalirudin-treated patients, there was no significant difference in major bleeding rates between patients with radial access and those with femoral access (1.8% vs. 3.1%; OR: 0.96; 95% CI: 0.65 to 1.41; p = 0.83; I² = 13.28%) (Figure 4). In contrast, in patients treated with heparin with or without GPIs, radial access use resulted in significant major bleeding reduction compared with femoral access (2.5% vs. 6%; OR: 0.57; 95% CI: 0.43 to 0.77; p < 0.001; I² = 0%).

**MACE at 30 days.** There were no significant differences in the incidence of MACE between radial and femoral access in patients treated with bivalirudin (1.6% vs. 1.7%; OR: 0.84; 95% CI: 0.31 to 2.23; p = 0.72; I² = 82.26%) (data not shown). In contrast, in patients treated with heparin with or without GPIs, there was a trend toward lower mortality with radial access compared with femoral access, but it was not statistically significant (1.82% vs. 1.85%; OR: 0.69; 95% CI: 0.48 to 1.00; p = 0.051; I² = 0%).

Visual inspection of funnel plots as well as Egger’s test did not suggest any publication bias. Funnel plots for major bleeding are shown in Online Figures 3 to 6.

**DISCUSSION**

The present meta-analysis is the first to provide a detailed evaluation of the interaction between
**FIGURE 3** Forest Plot Showing No Significant Difference in All-Cause Mortality Between Bivalirudin and Heparin in Patients With Femoral Access and Those With Radial Access

<table>
<thead>
<tr>
<th>Study name</th>
<th>Access</th>
<th>Events / Total</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUITY</td>
<td>Femoral</td>
<td>56 / 4004</td>
<td>1.08</td>
<td>0.74</td>
<td>1.58</td>
<td>0.39</td>
<td>0.698</td>
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<td>BRAVE-4</td>
<td>Femoral</td>
<td>7 / 269</td>
<td>1.02</td>
<td>0.35</td>
<td>2.96</td>
<td>0.04</td>
<td>0.967</td>
<td>5.5</td>
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<tr>
<td>EUROMAX</td>
<td>Femoral</td>
<td>22 / 558</td>
<td>1.29</td>
<td>0.68</td>
<td>2.42</td>
<td>0.78</td>
<td>0.437</td>
<td>15.1</td>
</tr>
<tr>
<td>ISAR-REACT 4</td>
<td>Femoral</td>
<td>14 / 858</td>
<td>1.17</td>
<td>0.54</td>
<td>2.55</td>
<td>0.40</td>
<td>0.691</td>
<td>10.2</td>
</tr>
<tr>
<td>MATRIX</td>
<td>Femoral</td>
<td>32 / 1812</td>
<td>0.66</td>
<td>0.42</td>
<td>1.03</td>
<td>-1.82</td>
<td>0.069</td>
<td>29.0</td>
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<tr>
<td>Overall</td>
<td></td>
<td>131 / 7501</td>
<td>0.96</td>
<td>0.75</td>
<td>1.24</td>
<td>-0.28</td>
<td>0.777</td>
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</tbody>
</table>

Heterogeneity: Q= 4.126, df= 4, p= 0.389, I²= 3.065%

**FIGURE 4** Forest Plot Showing That Radial Access Reduces Major Bleeding in Heparin-Treated Patients But Not in Bivalirudin-Treated Patients

<table>
<thead>
<tr>
<th>Study name</th>
<th>Anticoagulation</th>
<th>Events / Total</th>
<th>Odds ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
<th>Relative weight</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Bivalirudin</td>
<td>11 / 265</td>
<td>4.39</td>
<td>0.90</td>
<td>21.28</td>
<td>1.84</td>
<td>0.066</td>
<td>15.7</td>
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<td>EUROMAX</td>
<td>Bivalirudin</td>
<td>6 / 510</td>
<td>0.59</td>
<td>0.21</td>
<td>1.62</td>
<td>-1.03</td>
<td>0.304</td>
<td>28.3</td>
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<tr>
<td>HORIZONS-AMI</td>
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<td>1 / 102</td>
<td>1.00</td>
<td>0.06</td>
<td>16.22</td>
<td>0.00</td>
<td>1.000</td>
<td>6.0</td>
</tr>
<tr>
<td>MATRIX</td>
<td>Bivalirudin</td>
<td>27 / 1798</td>
<td>0.77</td>
<td>0.46</td>
<td>1.27</td>
<td>-1.02</td>
<td>0.308</td>
<td>49.9</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>42 / 2675</td>
<td>0.95</td>
<td>0.46</td>
<td>1.95</td>
<td>-0.14</td>
<td>0.890</td>
<td></td>
</tr>
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</table>

Heterogeneity: Q= 4.825, df= 3, p= 0.185, I²= 37.818%

CI = confidence interval; other abbreviations as in Table 1.
bivalirudin and radial access on outcomes in patients with ACS undergoing invasive approaches. We included 8 trials with a total of 27,491 patients. The main findings of our meta-analysis are as follows: 1) bivalirudin lowers major bleeding in patients with femoral access but not in those with radial access; 2) radial access lowers major bleeding in patients treated with heparin but not in patients treated with bivalirudin; and 3) there is no difference in MACE or all-cause mortality between bivalirudin and heparin with or without GPIs in patients with femoral access and those with radial access.

Radial access and bivalirudin use are 2 distinct strategies that have been increasingly used in an attempt to minimize the burden of major bleeding and accordingly improve outcomes in patients with ACS undergoing invasive approaches (9,14,30). However, whether the combined use of both strategies is more effective than either one alone is not clear.

Our access-based meta-analysis showed that compared with heparin, bivalirudin lowered major bleeding in patients with femoral access but not in those with radial access. Those findings were evident regardless of whether GPIs were used routinely or selectively with heparin. However, given the small number of studies included, more trials are needed to validate our findings. MACE and mortality, in contrast, were not different regardless of access site used. The absence of benefit with bivalirudin in patients with radial access can be explained by the fact that using radial access leads to substantial reduction of access-site bleeding, which constitutes a significant portion of major bleeding in patients with ACS. Hence, an additional benefit with bivalirudin becomes limited to nonaccess-site bleeding that fails to reach statistical significance because of the small number of events.

Our findings are in agreement with an analysis of data from the Blue Cross Blue Shield of Michigan Cardiovascular Consortium showing that the bleeding-reducing advantage of bivalirudin is attenuated by radial access use, especially when compared with heparin monotherapy (31). Conversely, analysis of data from the CathPCI registry showed that bivalirudin reduced major bleeding even when radial access was used and that the effect was driven by lowering nonaccess-site bleeding (32). However, the retrospective nature of the study and the possibility of the presence of unidentified confounding factors might have resulted in the contrast between that study and our meta-analyses.

In our anticoagulation-based meta-analysis, we compared radial access outcomes with those of femoral access in bivalirudin- and heparin-treated patients. Radial access resulted in major bleeding reduction in patients treated with heparin-based regimens but not in patients treated with bivalirudin. In a similar fashion to our access-based analysis, those findings can be explained by the lack of additional bleeding-reducing benefit of radial access if bleeding is already low in bivalirudin-treated patients.

In contrast, there were statistically nonsignificant trends toward lower rates of MACE ($p = 0.058$) and all-cause mortality ($p = 0.051$) with radial access in heparin-treated patients. These trends, however, were not evident in bivalirudin-treated patients. Analysis of previous RCTs showed that radial access use lowered mortality and MACE in patients with ACS (9), which is in agreement with our findings because heparin was the predominant anticoagulant agent used in those trials. The absence of statistical significance in our meta-analysis may be attributed to the small number of studies included.

The overall findings of the present meta-analysis suggest that there is no additional benefit when the 2 strategies to avoid bleeding, namely, radial access and bivalirudin, are used in combination as opposed to the use of either one alone. Therefore, the risks and benefits of each strategy need to be evaluated when making decisions regarding the best approach for patients with ACS.

**STUDY LIMITATIONS.** One limitation of the present meta-analysis is the small number of trials included to calculate the overall effects. Those studies were the only ones that stratified outcomes on the basis of access site. However, radial access was used mainly in the more recent trials, and most of those trials were included in our meta-analysis. Another limitation is that the only trial that was randomized on the basis of access site and anticoagulation was MATRIX (11,33). The remaining trials were randomized only on the basis of anticoagulation, not access site. Therefore, more trials are needed to validate our findings. Furthermore, the ongoing SAFARI-STEMI (Femoral Versus Radial Access for Primary PCI) (NCT01398254) randomized trial comparing outcomes in patients with radial access and those with femoral access when using bivalirudin for anticoagulation should provide further information on the feasibility of the combined use of radial access and bivalirudin. A third limitation is that other factors that might have influenced bleeding rates, such as vascular closure device use, the possibility that some operators had more experience with radial access than femoral access, and the possibility that
radial access was preferentially used in patients with lower baseline bleeding risk, were not reported in most trials and therefore were not accounted for in our meta-analysis.

CONCLUSIONS

Bivalirudin lowers major bleeding in patients with ACS with femoral access but not with radial access. In a similar fashion, radial access does not improve bleeding outcomes in bivalirudin-treated patients. Therefore, the combined use of these 2 bleeding-reducing modalities is not superior to using either one separately.

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REFERENCES


**KEY WORDS** acute coronary syndrome(s), bivalirudin, femoral access, heparin, radial access

**APPENDIX** For supplemental tables and figures, please see the online version of this article.